REMARKS

Claims

Claims 1-7, 9-10, 12-16, and 20–22 are currently under examination with claims 18-19 withdrawn from consideration due to restriction/election and claims 8, 11 and 17 cancelled without prejudice or disclaimer.

The allowability of claims 4 and 5 is gratefully acknowledged.

Claim amendments

The claims have been amended to use language in accordance with conventional US practice.

Support for the amendment of claim 1 and the claims dependent thereon can be found at, for example, page 33, ¶2 of the originally-filed specification. The Examiner is also requested to review the paragraph bridging pages 15 and 16 of the instant specification.

It is respectfully submitted that the claim amendments do not raise new matter.

Claim objections

The Examiner is thanked for his careful review of the claims. The objection of claims 1 and 3 are moot in view of the amendments. With respect to the substituents at R^2-R^5, Applicants respectfully submit that the claim language is consistent with Markush practice. Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. §102/§103(a) over Halazy

The PTO's allegation that the subject matter of claims 1-7, 9–10, 12-16 and 20–22 are anticipated, or in the alternate, rendered obvious by Halazy et al. (US 5,726,177) is respectfully traversed

Halazy discloses compounds having a mandatory C_2H_5-NR^5R^6 radical (with respect to the R^4 substituent), a carbonyl, SO_2 and/or oxo functionalized bridging moiety between the indole system and the piperazine ring (with respect to the X^1 substituent) and an optionally substituted mandatory phenyl moiety (with respect to the Z group). Thus, the compounds of the instant invention are structurally distinct from Halazy's compounds. Moreover, the cited reference does not teach compositions comprising Applicants' compounds. The cited reference thus fails to anticipate what is claimed herein. It is well-established that for anticipation, the reference has to

meet each and every element recited in Applicants' claims. Absent such teaching or guidance, there can be no anticipation. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102(a)/§103(a) over Bottcher

Claims 1–3, 4-7, 12–16 and 20–22 stand rejected under 35 U.S.C. §102(a) as being anticipated or rendered obvious by the newly-applied Bottcher references (US 6,838,461 and US 6,723,725). This contention is respectfully traversed.

Bottcher's compounds in the '725 patent are distinct from the compounds of the instant invention in at least the following respects:

(a) a mandatory CO-R^3 moiety (with respect to the substituent at R^4);

(b) a mandatory carbonyl bridge between the indole system and the piperazine ring(with respect to the substituent at X^1);

(c) a mandatory ethylene bridge between the piperazine ring and the R^1 group

(d) lack of anellated or bicyclic heterocyclic residue(s)

Bottcher's compounds in the '461 patent are distinct from the compounds of the instant invention in at least the following respects:

(a) presence of hydrogen (H) with respect to the substituent at R^4;

(b) a mandatory carbonyl bridge between the indole system and the piperazine ring (with respect to the substituent at X^1);

(c) a mandatory ethylene bridge between the piperazine ring and the R^1 group

(d) lack of anellated or bicyclic heterocyclic residue(s)

Since not all structural aspects of Applicants' compounds are taught by the cited references, the newly-applied Bottcher references (US 6,838,461 and US 6,723,725) cannot anticipate what is claimed by the instant invention. Withdrawal of the rejection is respectfully requested.

§103(a) rejections

The aforementioned Halazy and Bottcher references, either solely or in combination, also fail to render obvious the claims of the instant invention. At page 10 of the Office Action, it is alleged that "one would be motivated to employ the compounds/compositions of Halazy et al. to obtain the instant compounds/compositions of formula (I), wherein the variables R^2– R^5

independently is not substituted with a Het moiety thereof, the variables E and G together with the N atom to which they are bonded, are piperazine or piperidine thereof." At page 11, a similar argument is presented with respect to Boettcher's compounds. Applicants respectfully disagree with these contentions. The Office Action fails to present any evidence that the cited references, either solely or in combination, propose the change in structure as proposed by the Examiner. Absent such guidance, there can be no *prima facie* case for obviousness. See *In re Grabiak* F.2d at 732, 226 USPQ at 872 (Fed. Cir. 1985). Moreover, even if such knowledge were derived from secondary sources, there is no reasonable way to arrive at the claimed compounds under US law. See e.g., *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed.Cir. 1992). Withdrawal of the rejection is respectfully requested.

Double patenting

The non-statutory double patenting rejection of claims 1–7, 9, 10, 12–16 and 20–22 over the allegedly conflicting claims of the aforementioned Boettcher patents (US 6,838,461 and US 6,723,725) is moot in view of the aforementioned remarks and the amendments presented herein. Withdrawal of the rejection is respectfully requested.

Restriction

Applicants thank the Examiner for agreeing to examine previously withdrawn claims 20–22 on the merits. However, insofar as only a partial withdrawal of the restriction requirement was made, and claims 18–19 still remain restricted, the restriction requirement is respectfully traversed.

Page 2 of the Office Action concedes that "the entirety of the present claims possess unity of invention under 37 CFR §1.499," but proceeds to contend that the claims 1–7, 9, 10, 12–16 and 18–22 lack unity of invention. The Examiner cites Halazy and/or Chakravarty to bolster his lack of unity-of-invention contention. However, as established in the preceding paragraphs, the compounds taught by the cited references do not relate to the compounds of the instant invention.

Applicants cordially urge the Examiner to withdraw the restriction requirement insofar as all the claims in the application involve related subject matter, for example, a compound of formula I. A search of all the claims would comprise overlapping subject matter, and it would not be an undue burden on the Examiner to carry out a search. "If search and examination of an entire application can be made without serious burden, the examiner *must* examine it on the

merits, even though it includes claims to independent or distinct invention." (Emphasis added.) M.P.E.P. 803. The Office Action has not provided any reasons why a search and/or examination of all the claims in the application would result in undue burden. Accordingly, it is respectfully submitted that the restriction be withdrawn.

Applicants' petition against the restriction requirement (filed: June 19, 2007) was prematurely deemed moot in view of the Examiner's partial withdrawal of the restriction requirement. However, a complete reversal of this requirement, as requested in the petition, has not been made. As such, Applicants reserve the right request reconsideration of the petition if the requirement for restriction is maintained. However, in view of the aforementioned arguments and remarks, Applicants cordially request the Examiner to facilitate prosecution via withdrawal of the pending restriction requirement in its entirety.

The alleged requirement that Applicants "should amend the claims to read on the elected subject matter" is respectfully traversed since traversal of the restriction requirement was timely made and Applicants petition filed June 19, 2007 has not been fully considered. Withdrawal of the objection is courteously requested.

Rejections under 35 U.S.C. §112, ¶1

Claims 9–10 and 12–16 stand rejected under 35 U S.C. § 112, ¶1 for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Enablement

In the paragraphs bridging pages 5 and 6 of the Office Action, the Examiner contends that the "pharmaceutical art is unpredictable, requiring each embodiment to be *individually* assessed for *physiological* activity." This contention is without legal basis. The Office Action at page 5 further alleges that "there are no working examples present for the treatment of a disease mediated by 5-HT or inhibiting the activity of an excitatory amino acid in a cell by the administration of compounds of the instant invention." Applicants disagree with this statement.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the methods claimed herein are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt

that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, Applicants' specification teaches that compounds of the present invention are useful for practicing the methods claimed herein. See, for example, page 5, lines 20-24 and page 20, lines 19-21 of the instant specification, as originally filed. In this regard, Applicants' specification expressly teaches that substituted indole compounds, such as compounds of Formula I, serve as anti-psychotic agents because of their ability to inhibit important regulators of the 5HT receptor pharmacology (for example, 5HT agonistic and 5HT reuptake inhibitory activity). See, page 6, lines 15–25. Rationale for the use of the compounds of the instant invention in the treatment of diseases is also provided See, the paragraph bridging pages 5 and 6 and the paragraph bridging pages 6 and 7 of the specification, as originally filed

The PTO is cordially requested to review the cited references by Peglion et al. (US 6,486,171) and Halazy et al. (US 5,726,177). The teachings of these references and the experimental data contained therein *reasonably* corroborate Applicants' disclosure on the pharmaceutical activity of the claimed compounds and compositions thereof. In particular, in the paragraphs bridging cols. 21–22, Peglion teaches that a related class of piperidine compounds have affinity for the 5-HT receptor (Example 42) as well as inhibitory activity against serotonin reuptake (Example 41). Peglion teaches and also claims that the piperidine compounds are useful for treating 5-HT mediated diseases. See, the disclosure in col. 1, paragraphs 3–4 and claims 14 and 15 of Peglion. A similar disclosure is provided in the paragraphs bridging cols. 74–76 of Halazy et al. (US 5,726,177). Halazy describes the activity of a related class of indole-derived arylpiperazine compounds on the 5-HT receptor system. See the "STUDY OF THE AFFINITY" section in Halazy et al. and the data presented therein. The instant specification provides an enabling disclosure on the effect of claimed compounds on the 5-HT receptor system. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement based on the "unpredictability" and "lack of working examples" are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested

The contention that compounds should be assessed for their *physiological activity* is without legal basis Decades of scientific studies, both at the basic and clinical levels, have established that *in vitro* studies "reasonably correlate" with their *in vivo* counterparts. In this

regard, the Examiner is cordially invited to review the attached copy of *Fiebig et al.*, European Journal of Cancer, 40 (2004) 802-820, showing correlation of *in vitro* activity to *in vivo* activity as the basis for anticancer drug discovery. Moreover, Applicants' specification provides literature references which discuss techniques for the assessment of the claimed inhibitory activity *in vitro* and its correlation with *in vivo* pharmacology See, the entire disclosure contained in the paragraphs bridging page 7, line 29 to page 9, line 11 of the instant specification.

Furthermore, the patent law is in accord with the realities of pharmaceutical arts.

In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), discussed *supra* the court affirming the decision on reliance on *in vitro* data, and the decision stated that

> *in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

The court in *Cross* decision also noted the following

> Knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.
>
> ...
>
> Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.

The Federal Circuit in *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996), stated that

> all that is required is the test to be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Also, the court in *Bruna 51 F.3d 1560,* 34 USPQ2d 1436 (Fed. Cir. 1995) stated that

> it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure established the basic pharmacology for the compounds, but where no examples

were provided. The *Bundy* specification stated that the compounds of the invention possessed activity similar to E-type prostaglandins Nevertheless it was found that sufficient guidance as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of §112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Thus, neither the reality of the pharmaceutical arts or industry or the state of the law in this area provide basis for the broad allegations on pages 5 and 6 of the Office Action. Thus, the rejection is without merit and should be withdrawn.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No 13-3402.

Respectfully submitted,

Harry B. Shubin, Reg. No. 32,004
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone. (703) 243-6333
Facsimile: (703) 243-6410

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Encl:

- Feibig et al.